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DATE: Friday, September 24, 2004

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<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ</i>			
<input type="checkbox"/>	L13	L12 and enzyme	14
<input type="checkbox"/>	L12	L8 and aspartic	14
<input type="checkbox"/>	L11	L8 and aspartic enzyme	0
<input type="checkbox"/>	L10	L9 and aspart? enzyme	0
<input type="checkbox"/>	L9	L8 and cancer	15
<input type="checkbox"/>	L8	L6 and inhibit?	15
<input type="checkbox"/>	L7	L6 with inhibit?	0
<input type="checkbox"/>	L6	cathepsin D precursor	27
<input type="checkbox"/>	L5	L1 and metastatis	0
<input type="checkbox"/>	L4	L1 and cancer	1
<input type="checkbox"/>	L3	L1 and treat cancer	0
<input type="checkbox"/>	L2	L1 and protein fragments	1
<input type="checkbox"/>	L1	aspartic enzyme	14

END OF SEARCH HISTORY

=> d ibib hitseq abs tot

L2 ANSWER 1 OF 4 HCPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:241459 HCPLUS
DOCUMENT NUMBER: 132:275964
TITLE: Novel human aspartase homologous to cathepsin D precursor and use for producing anti-metastasis plasma protein fragments
INVENTOR(S): Morikawa, Wataru; Kaminaka, Kazuyoshi; Takemoto, Sumiyo; Maeda, Hiroaki; Nozaki, Chikateru; Miyamoto, Seiji
PATENT ASSIGNEE(S): Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020570	A1	20000413	WO 1999-JP5322	19990929
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2000106882	A2	20000418	JP 1998-296095	19981002
EP 1118660	A1	20010725	EP 1999-970118	19990929
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			JP 1998-296095	A 19981002
			WO 1999-JP5322	W 19990929

IT 254754-41-1

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(N-terminus of human aspartase PACE4 (plasminogen angiostatin converting enzyme of pH 4); novel human aspartase homologous to cathepsin D precursor and use for producing anti-metastasis plasma protein fragments)

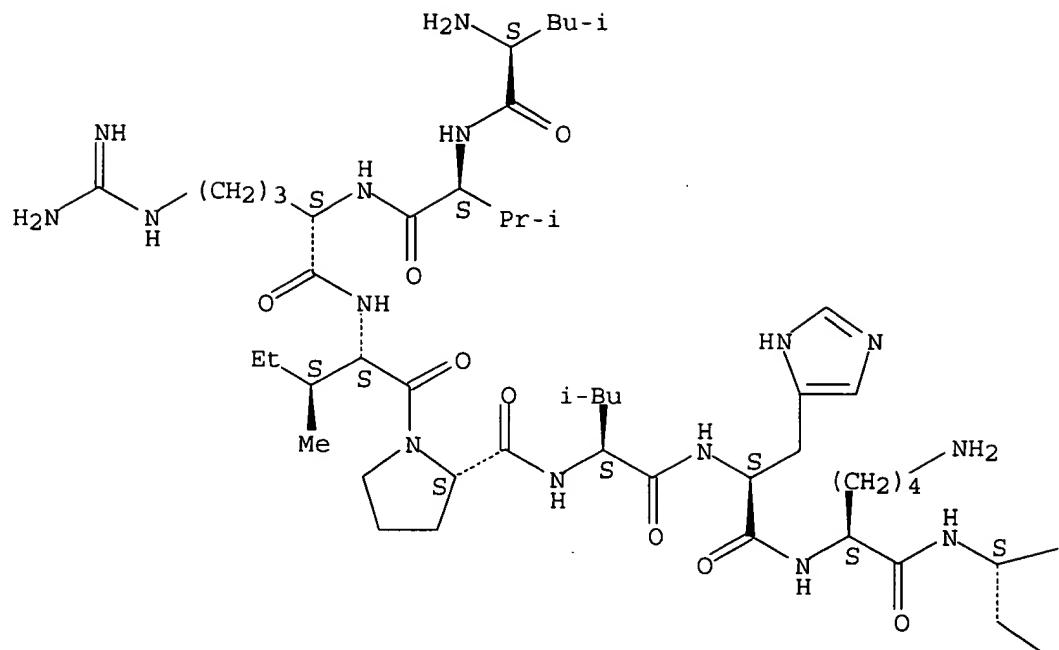
RN 254754-41-1 HCPLUS

CN L-Threonine, L-leucyl-L-valyl-L-arginyl-L-isoleucyl-L-prolyl-L-leucyl-L-histidyl-L-lysyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

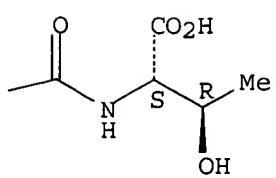
SEQ 1 LVRIPPLHKFT

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A

Ph

AB A novel aspartase, PACE4 (plasminogen angiostatin converting enzyme of pH 4), is prepared from cell line PC-3 that was established from human prostate cancer and characterized. PACE4 exhibits a mol. weight of 45 kDa as determined by

non-reducing SDS-PAGE and LVRIPPLHKFT at the N-terminus. PACE4 aspartase is highly homol. to human cathepsin D precursor and can degrade plasma proteins such as plasminogen, fibronectin, vitronectin, and human hepatic growth factor into fragments that have the angiostatin-like activities and thus the anti-metastasis effects. A pharmaceutical composition containing PACE4

for the prevention of treatment of solid cancers, diabetic retinopathy, or rheumatism is also claimed.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 4 HCPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:458339 HCPLUS

DOCUMENT NUMBER: 132:91503

TITLE: Modulation of Proliferation and Chemosensitivity by Procathepsin D and Its Peptides in Ovarian Cancer

AUTHOR(S): Bazzett, Lisa B.; Watkins, Christopher S.; Gercel-Taylor, Cicek; Taylor, Douglas D.

CORPORATE SOURCE: Departments of Obstetrics & Gynecology, University of Louisville School of Medicine, Louisville, KY, 40292, USA

SOURCE: Gynecologic Oncology (1999), 74(2), 181-187

CODEN: GYNOA3; ISSN: 0090-8258

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

IT 254754-41-1P

RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)

(Peptide 1, amino acids 21 to 30 of procathepsin D; modulation of proliferation and chemosensitivity by procathepsin D and peptides in human ovarian cancer)

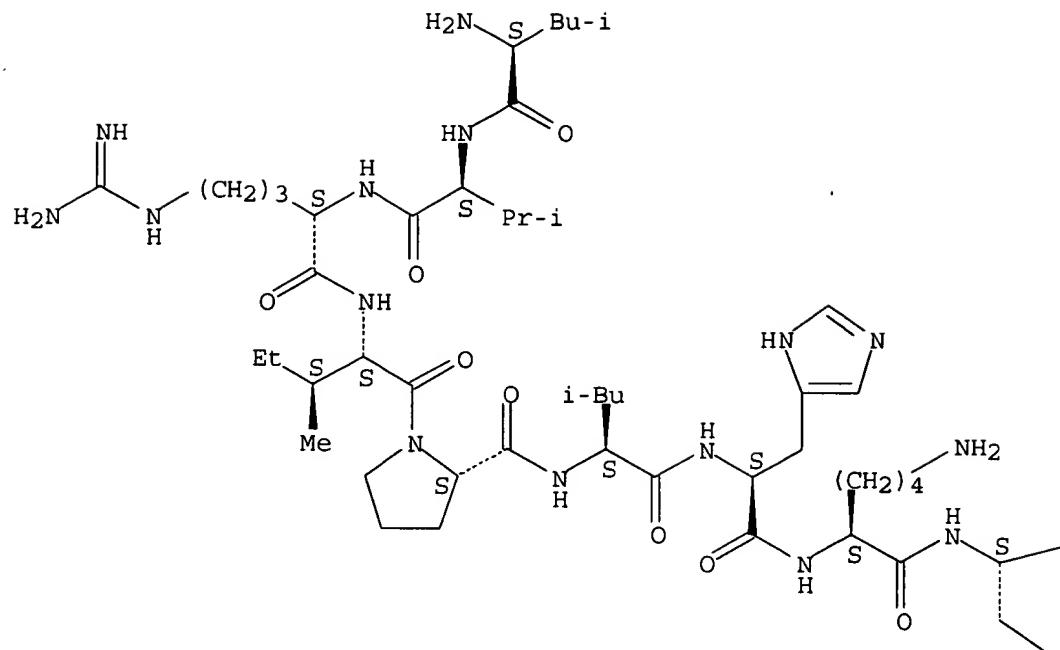
RN 254754-41-1 HCPLUS

CN L-Threonine, L-leucyl-L-valyl-L-arginyl-L-isoleucyl-L-prolyl-L-leucyl-L-histidyl-L-lysyl-L-phenylalanyl- (9CI) (CA INDEX NAME)

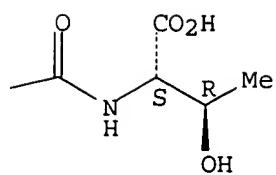
SEQ 1 LVRIPPLHKFT

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-A

Ph

AB Since the presence of precursors (pro-forms) of the aspartyl endoprotease, cathepsin D, appears to be linked with tumor progression, their presence was examined in sera and tumor tissues of ovarian cancer patients. The role of cathepsin D pro-forms was further assessed in the dysregulated proliferation and chemoresistance observed in advanced ovarian cancer. Cathepsin D was isolated from sera of ovarian cancer patients ($n = 20$) and normal volunteers ($n = 11$), as well as from solubilized normal ovarian epithelium ($n = 8$) and ovarian epithelial tumor tissue ($n = 12$). The specific mol. forms of cathepsin D were analyzed in these samples by Western immunoblot. Multiple circulating mol. weight forms of cathepsin D were identified in ovarian cancer patients ranging from 24 to 60 kDa, while in normal controls, a major band was observed at 34 kDa in all samples and minor bands corresponding to 27 and 48 kDa were detected in approx. half of the controls. To assess its consequences on ovarian cancer, the 52-kDa protein was immunopptd. from culture medium of an exponentially growing ovarian tumor cell line and was further purified by reverse-phase high-pressure liquid chromatog. Its effect on proliferation was assayed by determining cell doubling times and their chemosensitivity was measured in a standard cytotoxicity assay using cisplatin. In addition, decapeptides corresponding to the proportion of cathepsin D were analyzed in parallel. Procathepsin D and one decapeptide, peptide 2, as well as IGF-II (as a known pos.) increased cell proliferation, with doubling times of 28.4, 28.8, and 30.3 h, resp., vs. untreated UL-1 cells (36.4 h). Procathepsin D treatment of UL-1 tumor cells significantly increased the cisplatin LD₅₀ (74.9 $\mu\text{g/mL}$) over untreated (33.9 $\mu\text{g/mL}$) as well as IGF-II-treated (38.8 $\mu\text{g/mL}$) cells. Peptide 2 also showed a significant increase in LD₅₀ (69.5 $\mu\text{g/mL}$) compared to untreated and peptide 1-treated cells (37.1 $\mu\text{g/mL}$). There are several unique forms of cathepsin D expressed and accumulated by ovarian tumors and these forms are detectable in the sera of those with ovarian cancer. The presence of these procathepsin D can increase the proliferation of these tumor cells, while decreasing their sensitivity to chemotherapeutic agents. While procathepsin D and IGF-II both enhance proliferation, only procathepsin D (and peptide 2) appears to modulate chemosensitivity, suggesting a sep. receptor or pathway for this consequence. (c) 1999 Academic Press.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 4 HCPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:582912 HCPLUS

DOCUMENT NUMBER: 129:211700

TITLE: Method for inhibition of breast tumor growth by inhibition of procathepsin D activation peptide

INVENTOR(S): Fusek, Martin; Vetvicka, Vaclav

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA

SOURCE: U.S., 18 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5800814	A	19980901	US 1994-232997	19940422
PRIORITY APPLN. INFO.:			US 1994-232997	19940422

IT 212325-21-8
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(procathepsin D activation peptide inhibition for inhibition of breast tumor growth)
RN 212325-21-8 HCAPLUS
CN Glycine, L-leucyl-L-valyl-L-arginyl-L-isoleucyl-L-prolyl-L-leucyl-L-histidyl-L-lysyl-L-phenylalanyl-L-threonyl-L-seryl-L-isoleucyl-L-arginyl-L-arginyl-L-threonyl-L-methionyl-L-seryl-L-α-glutamyl-L-valylglycylglycyl-L-seryl-L-valyl-L-α-glutamyl-L-α-aspartyl-L-leucyl-L-isoleucyl-L-alanyl-L-lysylglycyl-L-prolyl-L-valyl-L-seryl-L-lysyl-L-tyrosyl-L-seryl-L-glutaminyl-L-alanyl-L-prolyl-L-alanyl-L-valyl-L-threonyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

SEQ 1 LVRIPLHKFT SIRRTMSEVG GSVEDLIAKG PVSKYSQAPA VTEG

AB Human procathepsin D was demonstrated to be mitogenic for breast cancer cells but not normal cells. The activation peptide of the procathepsin D appears to be responsible, since inhibition of enhancement of proliferation of breast cancer cells can be obtained by inhibition of the activation peptide through the use of an agent such as an antibody immunoreactive with the activation peptide.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:536377 HCAPLUS
DOCUMENT NUMBER: 103:136377
TITLE: Cloning and sequence analysis of cDNA for human cathepsin D
AUTHOR(S): Faust, Phyllis L.; Kornfeld, Stuart; Chirgwin, John M.
CORPORATE SOURCE: Sch. Med., Washington Univ., St. Louis, MO, 63110, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1985), 82(15), 4910-14
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

IT 98443-40-4

RL: PRP (Properties)
(amino acid sequence of)

RN 98443-40-4 HCAPLUS

CN Cathepsin D, pro- (human clone pHKCD45 protein moiety reduced) (9CI) (CA INDEX NAME)

SEQ 1 LVRIPLHKFT SIRRTMSEVG GSVEDLIAKG PVSKVSQAVP AVTEGPIPEV
51 LKNYMDAQYY GEIGIGTPQQ CFTVVFDTGS SNLWVPSIHC KLLDIACWIH
101 HKVNSDKSST VVKNGTSFDI HVGSGSLSGV LSQDTVSVPC QSASSASALG
151 GVKVERQVFG EATKQPGITF IAAKFDGIIG MAVPRISVNN VLPVFDNLMQ
201 QKLVDQNIIFS FVLSRDPDAQ PGGEMLGGT DSKVVKGSLS VLNVTRKAVW
251 QVHLDQVEVA SGLTLCKEGC EAIVDTGTSL MVGPVDEVRE LQKAIGAVPL
301 IQGEYMPIPCE KVSTLPAITL KLGGKGYKLS PEDYTLKVSQ AGKTLCLSGF
351 MGMDIPPPSG PLWILGDVFI GRYYTVFDRD NNRVGFAEAA RL

AB An 1110-base-pair cDNA clone for human cathepsin D was obtained by screening a λgt10 human hepatoma G2 cDNA library with a human renin exon 3 genomic fragment. Poly(A)+ RNA blot anal. with this cathepsin D

clone demonstrated a message length of .apprx.2.2 kilobases. The partial clone was used to screen a size-selected human kidney cDNA library, from which 2 cathepsin D recombinant plasmids with inserts of ≈2200 and 2150 base pairs were obtained. The nucleotide sequences of these clones and of the λgt10 clone were determined. The amino acid sequence predicted from the cDNA sequence shows that human cathepsin D consists of 412 amino acids with 20 and 44 amino acids in a pre- and a prosegment, resp. The mature protein region shows 87% amino acid identity with porcine cathepsin D but differs in having 9 addnl. amino acids. Two of these are at the terminus; the other 7 are positioned between the previously determined junction for the light and heavy chains of porcine cathepsin D. A high degree of sequence homol. was observed between human cathepsin D and other aspartyl proteases, suggesting a conservation of 3-dimensional structure in this family of proteins.

Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
***** HHHHHHHH SSSSSSS? ### Status: Signing onto Dialog *****
ENTER PASSWORD:
***** HHHHHHHH SSSSSSS? *****
Status: Login successfulWelcome to DIALOG

Dialog level 05.02.01D

Last logoff: 09may05 14:47:47
Logon file405 10may05 07:01:17
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***FDAnews (File 182)
***German Patents Fulltext (File 324)

***Beilstein Abstracts (File 393)
***Beilstein Facts (File 390)
***Beilstein Reactions (File 391)

RELOADED
***Medline (Files 154 & 155)
***ToxFile (File 156)

RESUMED UPDATING
***Canadian Business and Current Affairs (262)
***CorpTech (559)

REMOVED

***Health News Daily (43)
***FDC Reports Gold Sheet/Silver Sheet (184)
***FDC Reports (186/187)
***NDA Pipeline: New Drugs (189)

 >>> Enter BEGIN HOMEBASE for Dialog Announcements <<
 >>> of new databases, price changes, etc. <<

KWIC is set to 50.
HIGHLIGHT set on as '*'
PICKS is set ON as an alias for
5,159,143,358,340,344,348,447,73,155,349,266,10,34,434,42,43,50,65,71,91,94,14
4,198,304,370,467,444,357,156,157.
* * *

SYSTEM:HOME
Cost is in DialUnits
Menu System II: D2 version 1.7.9 term=ASCII
 *** DIALOG HOMEBASE(SM) Main Menu ***

Information:

1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)

5. Product Descriptions

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- 2. Database, Rates, & Command Descriptions
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Connections:

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/H = Help

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Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).

? B PICKS

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$0.02  TELNET
$0.02  Estimated cost this search
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SYSTEM:OS - DIALOG OneSearch
File 5:Biosis Previews(R) 1969-2005/May W1
(c) 2005 BIOSIS
File 159:Cancerlit 1975-2002/Oct
(c) format only 2002 Dialog Corporation
*File 159: Cancerlit is no longer updating.
Please see HELP NEWS159.
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File 143:Biol. & Agric. Index 1983-2005/Apr
(c) 2005 The HW Wilson Co
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File 358:Current BioTech Abs 1983-2005/Apr
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File 340:CLAIMS(R)/US Patent 1950-05/May 05
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***File 340: 2004 Reload is online as of October 6, 2004. Pricing changes effective October 1, 2004. See HELP NEWS 340 for details.**

File 344:Chinese Patents Abs Aug 1985-2004/May
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File 447:IMS Patent Focus 2005/Apr
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File 73:EMBASE 1974-2005/May W1
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File 34:SciSearch(R) Cited Ref Sci 1990-2005/May W1
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File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
(c) 1998 Inst for Sci Info

File 42:Pharmaceutical News Idx 1974-2005/Apr W4
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File 50:CAB Abstracts 1972-2005/Apr
(c) 2005 CAB International

File 65:Inside Conferences 1993-2005/May W2
(c) 2005 BLDSC all rts. reserv.

File 71:ELSEVIER BIOBASE 1994-2005/May W1
(c) 2005 Elsevier Science B.V.

File 91:MANTIS(TM) 1880-2005/Apr
2001 (c) Action Potential

File 94:JICST-EPlus 1985-2005/Mar W3
(c) 2005 Japan Science and Tech Corp(JST)

File 144:Pascal 1973-2005/May W1
(c) 2005 INIST/CNRS

File 198:Health Devices Alerts(R) 1977-2005/Feb W2
(c) 2005 ECRI-nonprft agncy

File 304:The Merck Index Online(SM) 2004/S2
(c) 2004 MERCK & CO. INC.

***File 304: File is now current to the 13th edition of The Merck Index**

File 370:Science 1996-1999/Jul W3
(c) 1999 AAAS

***File 370: This file is closed (no updates). Use File 47 for more current information.**

File 467:ExtraMED(tm) 2000/Dec
(c) 2001 Informania Ltd.

***File 467: F467 no longer updates; see Help News467.**

File 444:New England Journal of Med. 1985-2005/Apr W4
(c) 2005 Mass. Med. Soc.

File 357:Derwent Biotech Res. 1982-2005/May W2
(c) 2005 Thomson Derwent & ISI

File 156:ToxFile 1965-2005/May W1
(c) format only 2005 The Dialog Corporation

***File 156: ToxFile has been reloaded with the 2005 MeSH.**

Please see HELP NEWS 156 for details.
File 157:BIOSIS Toxicology (c) 2004 BIOSIS

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>>>Duplicate detection is not supported for File 340.
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>>>Duplicate detection is not supported for File 348.
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>>>Duplicate detection is not supported for File 349.
>>>Duplicate detection is not supported for File 198.
>>>Duplicate detection is not supported for File 304.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S2      15  RD (unique items)
? t s2/9/all
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2/9/1 (Item 1 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
(c) 2005 BIOSIS. All rts. reserv.

0014822064 BIOSIS NO.: 200400189750
Structure-based approaches to the development of novel anti-malarials.
AUTHOR: Brady R Leo (Reprint); Cameron Angus
AUTHOR ADDRESS: Department of Biochemistry, University of Bristol, Bristol,
BS9 3TD, UK**UK
AUTHOR E-MAIL ADDRESS: L.Brady@bris.ac.uk
JOURNAL: Current Drug Targets 5 (2): p137-149 February 2004 2004
MEDIUM: print
ISSN: 1389-4501 (ISSN print)
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 210756-42-6: 1-deoxy-D-xylulose 5-phosphate
reductoisomerase; 9024-52-6: aldolase; 220247-45-0: *aspartic acid
proteases*; 37353-41-6: cysteine proteases; 165587-69-9: cysteine
proteases; 9002-03-3: dihydrofolate reductase; 9001-50-7Q:
glyceraldehyde 3-phosphate dehydrogenase; 9028-92-6Q: glyceraldehyde
3-phosphate dehydrogenase; 37250-87-6Q: glyceraldehyde 3-phosphate
dehydrogenase; 162995-20-2Q: glyceraldehyde 3-phosphate dehydrogenase;
9001-50-7: glyceraldehyde 3-phosphate dehydrogenase; 14875-96-8: heme;
9001-60-9: lactate dehydrogenase; 81669-70-7: metalloproteinase;
369636-51-1: peptide deformylase; 9023-78-3: triosephosphate isomerase
ENZYME COMMISSION NUMBER: EC 1.1.1.267: 1-deoxy-D-xylulose 5-phosphate
reductoisomerase; EC 4.1.2.13: aldolase; EC 1.5.1.3: dihydrofolate
reductase; EC 1.2.1.12: glyceraldehyde 3-phosphate dehydrogenase; EC
1.1.1.27: lactate dehydrogenase; EC 3.4.24.21: metalloproteinase; EC
3.5.1.88: peptide deformylase; EC 5.3.1.1: triosephosphate isomerase
DESCRIPTORS:
MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics;
Methods and Techniques; Parasitology; Pharmacology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata,
Animalia; Sporozoa--Protozoa, Invertebrata, Animalia
ORGANISMS: human (Hominidae)--host; Plasmodium falciparum (Sporozoa)--

parasite
ORGANISMS: PARTS ETC: food vacuole
COMMON TAXONOMIC TERMS: Chordates; Humans; Mammals; Primates; Vertebrates ; Animals; Invertebrates; Microorganisms; Protozoans
DISEASES: malaria--blood and lymphatic disease, parasitic disease, drug therapy
MESH TERMS: Malaria (MeSH)
CHEMICALS & BIOCHEMICALS: 1-deoxy-D-xylulose 5-phosphate reductoisomerase; aldolase; *aspartic acid proteases *(plasmepsins)--drug target; cysteine proteases (falcipains)--drug target; dihydrofolate reductase; drug-enzyme complexes; enoyl reductase; glyceraldehyde 3-phosphate dehydrogenase; heme--degradation; isoprenoid synthesis inhibitors--antiinfective-drug, antiparasitic-drug, antiprotozoal-drug; lactate dehydrogenase; metabolic enzymes; metalloproteinase; novel anti-malarials--antiinfective-drug, antiparasitic-drug, antiprotozoal-drug, development; peptide deformylase; purine salvage inhibitors--antiinfective-drug, antiparasitic-drug, antiprotozoal-drug; triosephosphate isomerase
METHODS & EQUIPMENT: protein crystallography--crystallographic techniques , laboratory techniques
MISCELLANEOUS TERMS: fatty acid biosynthesis pathway; glycolytic pathway; inhibitor-protein contacts--improvement, visualization; protein prenylation; structure-based approaches; Literature Review
CONCEPT CODES:
10065 Biochemistry studies - Porphyrins and bile pigments
10802 Enzymes - General and comparative studies: coenzymes
12512 Pathology - Therapy
15006 Blood - Blood, lymphatic and reticuloendothelial pathologies
22002 Pharmacology - General
22005 Pharmacology - Clinical pharmacology
25502 Development and Embryology - General and descriptive
38502 Chemotherapy - General, methods and metabolism
38510 Chemotherapy - Antiparasitic agents
60502 Parasitology - General
60504 Parasitology - Medical
64002 Invertebrata: comparative, experimental morphology, physiology and pathology - Protozoa
BIOSYSTEMATIC CODES:
86215 Hominidae
35400 Sporozoa

2/9/2 (Item 2 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
(c) 2005 BIOSIS. All rts. reserv.

0013917457 BIOSIS NO.: 200200510968
Investigating the substrate specificity of HTLV-I protease
AUTHOR: Mariani Victoria (Reprint); Herger Bryan (Reprint); Shuker Suzanne B
AUTHOR ADDRESS: Department of Chemistry, Georgia Institute of Technology, Petite Institute for Bioengineering and Bioscience, 315 First Dr, Atlanta, GA, 30324, USA**USA
JOURNAL: Abstracts of Papers American Chemical Society 224 (1-2): pMEDI 204 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 224th National Meeting of the American Chemical Society Boston, MA, USA August 18-22, 2002; 20020818
ISSN: 0065-7727

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

DESCRIPTORS:

MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics;
Infection; Pharmacology

BIOSYSTEMATIC NAMES: Retroviridae--DNA and RNA Reverse Transcribing
Viruses, Viruses, Microorganisms

ORGANISMS: human T lymphotropic virus type 1 (Retroviridae)--pathogen

COMMON TAXONOMIC TERMS: DNA and RNA Reverse Transcribing Viruses;
Microorganisms; Viruses

CHEMICALS & BIOCHEMICALS: *aspartic acid protease*; enzyme inhibitor
drugs

MISCELLANEOUS TERMS: drug discovery; Meeting Abstract; Meeting Abstract

CONCEPT CODES:

00520 General biology - Symposia, transactions and proceedings

10802 Enzymes - General and comparative studies: coenzymes

12512 Pathology - Therapy

22002 Pharmacology - General

33506 Virology - Animal host viruses

36006 Medical and clinical microbiology - Virology

BIOSYSTEMATIC CODES:

03305 Retroviridae

2/9/3 (Item 3 from file: 5)

DIALOG(R) File 5:Biosis Previews(R)

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0013653988 BIOSIS NO.: 200200247499

**Endosomal proteolysis of internalized insulin at the C-terminal region of
the B chain by cathepsin D**

AUTHOR: Authier Francois (Reprint); Metiou Mourad; Fabrega Sylvie; Kouach
Mostafa; Briand Gilbert

AUTHOR ADDRESS: Faculte de Pharmacie Paris XI, INSERM U510, 5 Rue
Jean-Baptiste Clement, 92296, Chatenay-Malabry, France**France

JOURNAL: Journal of Biological Chemistry 277 (11): p9437-9446 March 15,
2002 2002

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The endosomal compartment of hepatic parenchymal cells contains an acidic endopeptidase, endosomal acidic insulinase, which hydrolyzes internalized insulin and generates the major primary end product A1-21-B1-24 insulin resulting from a major cleavage at residues PheB24-PheB25. This study addresses the nature of the relevant endopeptidase activity in rat liver that is responsible for most receptor-mediated insulin degradation in vivo. The endosomal activity was shown to be aspartic acid protease cathepsin D (CD), based on biochemical similarities to purified CD in 1) the rate and site of substrate cleavage, 2) pH optimum, 3) sensitivity to pepstatin A, and 4) binding to pepstatin A-agarose. The identity of the protease was immunologically confirmed by removal of greater than 90% of the insulin-degrading activity associated with an endosomal lysate using polyclonal antibodies to CD. Moreover, the elution profile of the endosomal acidic insulinase activity on a gel-filtration TSK-GEL G3000 SWXL high performance liquid

chromatography column corresponded exactly with the elution profile of the immunoreactive 45-kDa mature form of endosomal CD. Using nondenaturing immunoprecipitation and immunoblotting procedures, other endosomal aspartic acid proteases such as cathepsin E and beta-site amyloid precursor protein-cleaving enzyme (BACE) were ruled out as candidate enzymes for the endosomal degradation of internalized insulin. Immunofluorescence studies showed a largely vesicular staining pattern for internalized insulin in rat hepatocytes that colocalized partially with CD. In vivo pepstatin A treatment was without any observable effect on the insulin receptor content of endosomes but augmented the phosphotyrosine content of the endosomal insulin receptor after insulin injection. These results suggest that CD is the endosomal acidic insulinase activity which catalyzes the rate-limiting step of the in vivo cleavage at the PheB24-PheB25 bond, generating the inactive A1-21-B1-24 insulin intermediate.

REGISTRY NUMBERS: 9025-26-7: cathepsin D

DESCRIPTORS:

MAJOR CONCEPTS: Digestive System--Ingestion and Assimilation; Enzymology
--Biochemistry and Molecular Biophysics; Methods and Techniques

BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata,
Animalia

ORGANISMS: Sprague-Dawley rat (Muridae)--male

ORGANISMS: PARTS ETC: hepatic parenchymal cells--digestive system,
endosomal compartment; liver--digestive system

COMMON TAXONOMIC TERMS: Animals; Chordates; Mammals; Nonhuman Vertebrates
; Nonhuman Mammals; Rodents; Vertebrates

CHEMICALS & BIOCHEMICALS: cathepsin D--analysis, *aspartic acid
protease*, endosomal acidic insulinase, insulin endosomal processing
role; insulin A chain--analysis, endosomal proteolysis, separation;
insulin B chain--analysis, endosomal proteolysis, separation;
internalized insulin--B chain carboxyl-terminal region, analysis,
endosomal proteolysis, receptor-mediated degradation, separation

METHODS & EQUIPMENT: Beckman Coulter System Gold model 127 liquid
chromatograph--Beckman Coulter, laboratory equipment; gel filtration
TSK-GEL G3000 SWXL high-performance liquid chromatography column--Tosoh
Corp., laboratory equipment; gel-filtration high performance liquid
chromatography--Chromatographic Techniques, separation method;
immunoblotting--Immunologic Techniques, detection method;
immunofluorescence--Immunologic Techniques, detection method;
immunoprecipitation--isolation method, precipitation; reverse-phase
high performance liquid chromatography (RP-HPLC)--Chromatographic
Techniques, separation method

CONCEPT CODES:

02506 Cytology - Animal

10802 Enzymes - General and comparative studies: coenzymes

14004 Digestive system - Physiology and biochemistry

BIOSYSTEMATIC CODES:

86375 Muridae

2/9/4 (Item 4 from file: 5)

DIALOG(R) File 5:Biosis Previews(R)

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0012903989 BIOSIS NO.: 200100075828

Functional analysis of beta-secretase using mutagenesis and structural
homology modeling

AUTHOR: McConlogue L C (Reprint); Agard D A; Ota M; Sinha S; Anderson J;

Basi G; Jacobson-Croak K; Chilcote T; Tatsuno G
AUTHOR ADDRESS: Elan Pharmaceuticals, S San Francisco, CA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2): pAbstract No.-14.2
2000 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000; 20001104
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Proteolytic processing of the amyloid precursor protein by beta and gamma secretases leads to the formation Abeta peptide, the major component of Alzheimer's disease plaques. The purification and cloning of betasecretase indicates that it is a novel aspartic acid protease. betasecretase is rate-limiting for the production of Abeta and therefore is an excellent target for therapeutic intervention in AD. Here we describe mutagenesis and homology modeling of betasecretase to investigate functional and structural aspects of this protein. Mutagenesis of both putative active site aspartates, led to overexpression of inactive enzyme which was correctly processed from the pro-enzyme to the mature enzyme as determined by amino acid sequencing. Over-expression of these mutants did not reduce endogenous betasecretase activity. Based on the homology of betasecretase sequence to related aspartic acid proteases, some conserved cysteine residues are missing and novel cysteine residues are found. C278, C380, C330 are conserved with C330 predicted by homology to form a disulfide bond with C380. We have generated a structural model based on the crystal structure of Atlantic cod pepsin. C216 and C420 are novel cysteines that based on the modeled structure are close enough to be involved in disulfide bonding. Cysteines at positions 216, 278, 330, 380, 420 were replaced with alanines by mutagenesis and enzymatic assay of expressed protein showed that all of these cysteines are required for optimal betasecretase enzymatic activity.

REGISTRY NUMBERS: 158736-49-3: beta-secretase; 9001-75-6: pepsin

DESCRIPTORS:

MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics; Nervous System--Neural Coordination

BIOSYSTEMATIC NAMES: Osteichthyes--Pisces, Vertebrata, Chordata, Animalia

ORGANISMS: Atlantic cod (Osteichthyes)

COMMON TAXONOMIC TERMS: Animals; Chordates; Fish; Nonhuman Vertebrates; Vertebrates

DISEASES: Alzheimer's disease--behavioral and mental disorders, nervous system disease

MESH TERMS: Alzheimer Disease (MeSH)

CHEMICALS & BIOCHEMICALS: amyloid beta-peptide--proteolytic processing; amyloid precursor protein--proteolytic processing; beta-secretase--*aspartic acid protease*, functional analysis; pepsin

METHODS & EQUIPMENT: amino acid sequencing--sequencing method

MISCELLANEOUS TERMS: Meeting Abstract; Meeting Abstract

CONCEPT CODES:

10802 Enzymes - General and comparative studies: coenzymes
00520 General biology - Symposia, transactions and proceedings
10064 Biochemistry studies - Proteins, peptides and amino acids
20504 Nervous system - Physiology and biochemistry
20506 Nervous system - Pathology

BIOSYSTEMATIC CODES:

85206 Osteichthyes

2/9/5 (Item 5 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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0012028708 BIOSIS NO.: 199900288368

HTLV-I protease, reverse transcriptase, and integrase: The viral enzymes of replication

AUTHOR: Ikeda Richard A (Reprint); Ding Y Shirley (Reprint); Ha Julie (Reprint); Lal Renu B; Owen S Michele

AUTHOR ADDRESS: School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, 30332-0400, USA**USA

JOURNAL: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 20 (4): pA18 April 4, 1999 1999

MEDIUM: print

CONFERENCE/MEETING: Ninth International Conference on Human Retrovirology HTLV and Related Viruses Kagoshima, Japan April 5-9, 1999; 19990405

ISSN: 1077-9450

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

REGISTRY NUMBERS: 52350-85-3: integrase; 9068-38-6: reverse transcriptase

DESCRIPTORS:

MAJOR CONCEPTS: Enzymology--Biochemistry and Molecular Biophysics

CHEMICALS & BIOCHEMICALS: *aspartic acid protease*; integrase; reverse transcriptase; simian sarcoma virus reverse transcriptase; Gibbon ape leukemia virus reverse transcriptase; HTLV-I protease {human T-cell leukemia virus type I protease}--characterization, cloning; HTLV-I proteins--characterization, cloning

MISCELLANEOUS TERMS: Meeting Abstract; Meeting Abstract

CONCEPT CODES:

33506 Virology - Animal host viruses

10808 Enzymes - Physiological studies

00520 General biology - Symposia, transactions and proceedings

2/9/6 (Item 6 from file: 5)

DIALOG(R) File 5:Biosis Previews(R)
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0011963044 BIOSIS NO.: 199900222704

Solid-phase synthesis of potential aspartic acid protease inhibitors containing a hydroxyethylamine isostere

AUTHOR: Zhou Jinglan (Reprint); Termin Andreas; Wayland Melissa; Tarby Christine M

AUTHOR ADDRESS: Department of Medicinal Chemistry, CombiChem, Inc., 9050 Camino Santa Fe, San Diego, CA, 92121, USA**USA

JOURNAL: Tetrahedron Letters 40 (14): p2729-2732 April 2, 1999 1999

MEDIUM: print

ISSN: 0040-4039

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: A series of 1,3-diamino-2-propanol derivatives have been synthesized on solid phase as potential aspartic acid protease inhibitors. The developed methodology allows the incorporation of either

an alkyl group or H at the R2 site of hydroxyethylamine isostere.

DESCRIPTORS:

MAJOR CONCEPTS: Methods and Techniques; Pharmacology

CHEMICALS & BIOCHEMICALS: *aspartic acid protease*;

1,3-diamino-2-propanol derivatives--enzyme inhibitor,

hydroxyethylamine isostere containing, protease inhibitor, synthesis

METHODS & EQUIPMENT: chemical synthesis protocol--synthetic method;

solid-phase synthesis--synthetic method

MISCELLANEOUS TERMS: medicinal chemistry

CONCEPT CODES:

22002 Pharmacology - General

10050 Biochemistry methods - General

10502 Biophysics - General

38506 Chemotherapy - Antiviral agents

10802 Enzymes - General and comparative studies: coenzymes

2/9/7 (Item 7 from file: 5)

DIALOG(R) File 5:Biosis Previews(R)

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0011093292 BIOSIS NO.: 199799727352

Discovery of antifungal agents from natural sources: Virulence factor targets

AUTHOR: Clark Alice M; Walker Larry A

AUTHOR ADDRESS: Natl. Cent. Dev. Natural Products, Dep. Pharmacognosy,
Univ. Mississippi Sch. Pharmacy, University, MS 38677, USA**USA

JOURNAL: Abstracts of Papers American Chemical Society 214 (1-2): pAGRO
123 1997 1997

CONFERENCE/MEETING: 214th American Chemical Society National Meeting Las
Vegas, Nevada, USA September 7-11, 1997; 19970907

ISSN: 0065-7727

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

REGISTRY NUMBERS: 9002-10-2: PHENOLOXIDASE

DESCRIPTORS:

MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Enzymology--
Biochemistry and Molecular Biophysics; Pharmacognosy--Pharmacology;
Pharmacology

BIOSYSTEMATIC NAMES: Fungi Imperfecti or Deuteromycetes--Fungi, Plantae

ORGANISMS: Candida sp. (Fungi Imperfecti or Deuteromycetes); Cryptococcus
neoformans (Fungi Imperfecti or Deuteromycetes)

COMMON TAXONOMIC TERMS: Fungi; Microorganisms; Nonvascular Plants; Plants

CHEMICALS & BIOCHEMICALS: PHENOLOXIDASE

MISCELLANEOUS TERMS: ACTIVITY; ANTIFUNGAL AGENTS; *ASPARTIC ACID
PROTEASE*; BIOCHEMISTRY AND BIOPHYSICS; PHARMACOGNOSY; PHENOLOXIDASE;
SECRETION; VIRULENCE FACTOR TARGETS; Meeting Abstract

CONCEPT CODES:

00520 General biology - Symposia, transactions and proceedings

10060 Biochemistry studies - General

10502 Biophysics - General

22002 Pharmacology - General

38502 Chemotherapy - General, methods and metabolism

51518 Plant physiology - Enzymes

51522 Plant physiology - Chemical constituents

54000 Pharmacognosy and pharmaceutical botany

BIOSYSTEMATIC CODES:

15500 Fungi Imperfecti or Deuteromycetes

2/9/8 (Item 8 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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0011084276 BIOSIS NO.: 199799718336

The design and synthesis of nonpeptide peptidomimetics: From neuropeptide hormone agonists and antagonists to inhibitors of aspartic acid proteases

AUTHOR: Smith Amos B Iii

AUTHOR ADDRESS: Dep. Chem., Univ. Pa., Philadelphia, PA 19104, USA**USA

JOURNAL: FASEB Journal 11 (9): pA831 1997 1997

CONFERENCE/MEETING: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology San Francisco, California, USA August 24-29, 1997; 19970824

ISSN: 0892-6638

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

REGISTRY NUMBERS: 38916-34-6Q: SOMATOSTATIN; 51110-01-1Q: SOMATOSTATIN; 33507-63-0: SUBSTANCE P

DESCRIPTORS:

MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Metabolism

CHEMICALS & BIOCHEMICALS: SOMATOSTATIN; SUBSTANCE P

MISCELLANEOUS TERMS: AMINO ACID; *ASPARTIC ACID PROTEASE*; BIOCHEMISTRY

AND BIOPHYSICS; DESIGN; NONPEPTIDE PEPTIDOMIMETICS; PEPTIDE;

SOMATOSTATIN; SUBSTANCE P; SYNTHESIS; TRISPYRROLINONE 1; Meeting

Abstract

CONCEPT CODES:

00520 General biology - Symposia, transactions and proceedings

10060 Biochemistry studies - General

13002 Metabolism - General metabolism and metabolic pathways

2/9/9 (Item 9 from file: 5)

DIALOG(R) File 5:Biosis Previews(R)

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0010863164 BIOSIS NO.: 199799497224

Design and synthesis of pyrrolinone based non-peptidal peptidomimetics:

From beta-sheet mimetics to an orally active HIV-1 protease inhibitor

AUTHOR: Smith Amos B Iii (Reprint); Favor David A (Reprint); Guzman Mark C (Reprint); Pasternak Alexander (Reprint); Benowitz Andrew B (Reprint); Huff Joel R; Kuo Lawerance; Darke Paul L; Chen Zhongguo; Emini Emilio A; Sprengeler Paul A (Reprint); Hirschmann Ralph (Reprint)

AUTHOR ADDRESS: Dep. Chem., Univ. Pennsylvania, Philadelphia, PA 19104, USA **USA

JOURNAL: Abstracts of Papers American Chemical Society 213 (1-3): pORGN 51 1997 1997

CONFERENCE/MEETING: 213th National Meeting of the American Chemical Society San Francisco, California, USA April 13-17, 1997; 19970413

ISSN: 0065-7727

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

REGISTRY NUMBERS: 37205-61-1: PROTEASE INHIBITOR

DESCRIPTORS:

MAJOR CONCEPTS: Biochemistry and Molecular Biophysics; Enzymology--
Biochemistry and Molecular Biophysics; Methods and Techniques;
Microbiology
BIOSYSTEMATIC NAMES: Retroviridae--DNA and RNA Reverse Transcribing
Viruses, Viruses, Microorganisms
ORGANISMS: human immunodeficiency virus type 1 (Retroviridae)
COMMON TAXONOMIC TERMS: DNA and RNA Reverse Transcribing Viruses;
Microorganisms; Viruses
CHEMICALS & BIOCHEMICALS: PROTEASE INHIBITOR
MISCELLANEOUS TERMS: *ASPARTIC ACID PROTEASE*; BETA-SHEET MIMETICS;
BIOCHEMISTRY AND BIOPHYSICS; CHEMICAL SYNTHESIS; ENZYME INHIBITOR
SYNTHESIS; METHODOLOGY; SYNTHETIC METHOD; X-RAY STRUCTURE; 3,5-LINKED
POLYPYRROLINONES; Meeting Abstract
CONCEPT CODES:
00520 General biology - Symposia, transactions and proceedings
10050 Biochemistry methods - General
10504 Biophysics - Methods and techniques
10506 Biophysics - Molecular properties and macromolecules
10806 Enzymes - Chemical and physical
33506 Virology - Animal host viruses
BIOSYSTEMATIC CODES:
03305 Retroviridae

2/9/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0010225768 BIOSIS NO.: 199698693601
**The inhibitory effects of the cysteine protease inhibitor, oryzacystatin,
on digestive proteases and on larval survival and development of the
southern corn rootworm (*Diabrotica undecimpunctata howardi*)**
AUTHOR: Edmonds Heather S; Gatehouse Laurence N; Hilder Vaughan A;
Gatehouse John A
AUTHOR ADDRESS: Dep. Biol. Sci., Univ. Durham, South Rd., DH1 3LE, UK**UK
JOURNAL: Entomologia Experimentalis et Applicata 78 (1): p83-94 1996 1996
ISSN: 0013-8703
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: At least eight proteolytic activities have been identified in the midgut contents of larval Southern corn rootworm (*Diabrotica undecimpunctata howardi*). Around 70% of protease activity could be arrested by the cysteine protease inhibitors E-64 and chicken egg-white cystatin, while the aspartic acid protease inhibitor pepstatin caused 30% inhibition. The cysteine protease activity was found to be highly sensitive to inhibition by both chicken egg-white cystatin and the rice cystatin, oryzacystatin 1. Oryzacystatin 1, expressed as a fully functional fusion protein in *E. coli*, was found to strongly inhibit larval gut protease activity. This recombinant oryzacystatin, incorporated into artificial diet at concentrations of 10 mM and above, caused significant decreases in larval survival and weight gain. E-64 was also shown to cause a significant antimetabolic *in vivo* effect. These results demonstrate the great potential for cysteine protease inhibitors, such as oryzacystatin, as tools for exploitation in the control of the Southern corn rootworm.

REGISTRY NUMBERS: 37353-41-6: CYSTEINE PROTEASE; 121273-67-4: ORYZACYSTATIN

; 9014-01-1: PROTEASES; 81989-95-9: CYSTATIN; 26305-03-3Q: PEPSTATIN;
39324-30-6Q: PEPSTATIN

DESCRIPTORS:

MAJOR CONCEPTS: Development; Digestive System--Ingestion and Assimilation
; Economic Entomology; Enzymology--Biochemistry and Molecular
Biophysics; Metabolism; Pest Assessment Control and Management;
Physiology

BIOSYSTEMATIC NAMES: Coleoptera--Insecta, Arthropoda, Invertebrata,
Animalia; Lepidoptera--Insecta, Arthropoda, Invertebrata, Animalia

ORGANISMS: Diabrotica undecimpunctata howardi (Coleoptera); Lepidoptera
(Lepidoptera)

COMMON TAXONOMIC TERMS: Animals; Arthropods; Insects; Invertebrates

CHEMICALS & BIOCHEMICALS: CYSTEINE PROTEASE; ORYZACYSTATIN; PROTEASES;
CYSTATIN; PEPSTATIN

MISCELLANEOUS TERMS: ANTIMETABOLIC EFFECT; *ASPARTIC ACID PROTEASE
INHIBITOR*; CYSTATIN; PEPSTATIN; PEST CONTROL; WEIGHT GAIN

CONCEPT CODES:

10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10808 Enzymes - Physiological studies
13002 Metabolism - General metabolism and metabolic pathways
14006 Digestive system - Pathology
25508 Development and Embryology - Morphogenesis
54600 Pest control: general, pesticides and herbicides
60004 Economic entomology - Field, flower and truck crops
60016 Economic entomology - Chemical
64076 Invertebrata: comparative, experimental morphology, physiology and
pathology - Insecta: physiology

BIOSYSTEMATIC CODES:

75304 Coleoptera
75330 Lepidoptera

2/9/11 (Item 1 from file: 73)

DIALOG(R) File 73:EMBASE

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13026069 EMBASE No: 2005086563

**Overexpression of PCSK9 accelerates the degradation of the LDLR in a
post-endoplasmic reticulum compartment**

Maxwell K.N.; Fisher E.A.; Breslow J.L.

J.L. Breslow, Lab. of Biochem. Genet. and Metab., Rockefeller University,
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AUTHOR EMAIL: breslow@rockefeller.edu

Proceedings of the National Academy of Sciences of the United States of
America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 08 FEB 2005
, 102/6 (2069-2074)

CODEN: PNASA ISSN: 0027-8424

DOCUMENT TYPE: Journal ; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 56

Proprotein convertase subtilisin kexin 9 (PCSK9) is a member of the
subtilisin serine protease family with an important role in cholesterol
metabolism. PCSK9 expression is regulated by dietary cholesterol in mice
and cellular sterol levels in cell culture via the sterol regulatory
element binding protein transcription factors, and mutations in PCSK9 are
associated with a form of autosomal dominant hypercholesterolemia.
Overexpression of PCSK9 in mice leads to increased total and low-density

lipoprotein (LDL) cholesterol levels because of a decrease in hepatic LDL receptor (LDLR) protein with normal mRNA levels. To study the mechanism, PCSK9 was overexpressed in human hepatoma cells, HepG2, by adenovirus. Overexpression of PCSK9 in HepG2 cells caused a decrease in whole-cell and cell-surface LDLR levels. PCSK9 Overexpression had no effect on LDLR synthesis but caused a dramatic increase in the degradation of the mature LDLR and a lesser increase in the degradation of the precursor LDLR. In contrast, overexpression of a catalytically inactive mutant PCSK9 prevented the degradation of the mature LDLR; whereas increased degradation of the precursor LDLR still occurred. The PCSK9-induced degradation of the LDLR was not affected by inhibitors of the proteasome, lysosomal cysteine proteases, aspartic acid proteases, or metalloproteases. The PCSK9-induced degradation of the LDLR was shown to require transport out of the endoplasmic reticulum. These results indicate that overexpression of PCSK9 induces the degradation of the LDLR by a nonproteasomal mechanism in a post-endoplasmic reticulum compartment.

DRUG DESCRIPTORS:

*serine proteinase; *low density lipoprotein receptor sterol regulatory element binding protein; proteasome inhibitor; cysteine proteinase inhibitor; proteinase inhibitor; metalloproteinase inhibitor; unclassified drug

MEDICAL DESCRIPTORS:

*protein degradation; *hypercholesterolemia endoplasmic reticulum; cholesterol metabolism; protein expression; cholesterol intake; cell culture; autosomal dominant disorder; cell strain HepG2; adenovirus vector; cell surface; protein synthesis; protein transport; human; controlled study; human cell; article; priority journal DRUG TERMS (UNCONTROLLED): proprotein convertase subtilisin kexin 9; *aspartic acid protease inhibitor*

CAS REGISTRY NO.: 37259-58-8 (serine proteinase); 37205-61-1 (proteinase inhibitor)

SECTION HEADINGS:

029 Clinical and Experimental Biochemistry

2/9/12 (Item 1 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
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11468686 Genuine Article#: 657JW Number of References: 30

Title: Differential regulation by ambient pH of putative virulence factor secretion by the phytopathogenic fungus *Botrytis cinerea*

Author(s): Manteau S; Abouna S; Lambert B; Legendre L (REPRINT)

Corporate Source: Univ Western Sydney,Ctr Hort & Plant Sci, Penrith/NSW 1797/Australia/ (REPRINT); Univ Western Sydney,Ctr Hort & Plant Sci, Penrith/NSW 1797/Australia/; Univ Reims, Lab Plant Biol & Physiol, Plant Biochem & Mol Biol Res Unit, URVVC EA 2069, F-51687 Reims 2//France/

Journal: FEMS MICROBIOLOGY ECOLOGY, 2003, V43, N3 (APR 1), P359-366

ISSN: 0168-6496 Publication date: 20030401

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS

Language: English Document Type: ARTICLE

Geographic Location: Australia; France

Journal Subject Category: MICROBIOLOGY

Abstract: The fungal pathogen *Botrytis cinerea* is capable of developing on a wide variety of host plants that differ greatly in their pH values and biochemical defences. To evaluate whether the pH of the host tissue can regulate the production of pathogenicity factors by this fungus, we

examined the ability of two isolates of *B. cinerea* that originated from different plant species to secrete putative virulence elements on synthetic media buffered at pH 2.0 to pH 7.0. Even though differing in the intensity of their responses, both isolates reacted similarly to their ambient pH. The production of extracellular polysaccharides and oxalic acid was detectable above pH 4.0 and pH 5.0 respectively. Conversely, the production of aspartic acid proteases could only be seen between pH 3.0 and 4.0. Finally, the secretion of polygalacturonase and laccase activity was found to exhibit two maxima, one around pH 3.1 and one around pH 6.0. Thus, pathogenicity factor production was found to be minimal between pH 4.5 and 5.5 and a different set of factors was produced at pH 3.1 and 6.0, two values that were found to correspond respectively to the average host fruit and leaf pH. These results demonstrate that ambient pH differentially regulates the synthesis of pathogenicity factors by *Botrytis* and may act as a novel regulatory element to assist this fungus in tuning its virulence machinery to the composition of its host tissue. (C) 2002 Published by Elsevier Science B.V. on behalf of the Federation of European Microbiological Societies.

Descriptors--Author Keywords: *Botrytis cinerea* ; laccase ; polygalacturonase ; *aspartic acid protease ;* oxalic acid ; pH

Identifiers--KeyWord Plus(R): GENE-EXPRESSION; ASPERGILLUS-NIDULANS; TRANSCRIPTION FACTOR; ENVIRONMENTAL PH; CANDIDA-ALBICANS; ACID; INDUCTION; GROWTH; ACTIVATION; BERRIES

Cited References:

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BELLOCQ A, 1998, V273, P5086, J BIOL CHEM
BLANKENHORN D, 1999, V181, P2209, J BACTERIOL
CADDICK MX, 1986, V203, P346, MOL GEN GENET
DENISON SH, 2000, V29, P61, FUNGAL GENET BIOL
DERCKEL JP, 1998, V104, P56, PHYSIOL PLANTARUM
DERCKEL JP, 1999, V89, P197, PHYTOPATHOLOGY
GILAD NL, 2001, V199, P109, FEMS MICROBIOL LETT
GIRAUD T, 1997, V14, P1177, MOL BIOL EVOL
GRASSIN C, 1989, V48, P369, J SCI FOOD AGR
JARVIS WR, 1977, V15, MONOGRAPH AGR CANADA
JONES LJ, 1997, V251, P144, ANAL BIOCHEM
KAMOEN O, 1985, V50, P1053, MED FAC LANDBOUW RIJ
KAMOEN O, 1992, P39, RECENT ADV BOTRYTIS
LI WS, 1997, V145, P63, GENETICS
MACCLELLAN WD, 1973, V63, P1151, PHYTOPATHOLOGY
MACRAE WD, 1988, V71, P339, GENE
NAIR NG, 1993, V97, P1012, MYCOL RES
OLSON ER, 1993, V8, P5, MOL MICROBIOL
PORTA A, 1999, V181, P7516, J BACTERIOL
RAMON AM, 1999, V181, P7524, J BACTERIOL
SHI Q, 1999, V5, P3711, CLIN CANCER RES
SLOMCZYNSKI D, 1995, V61, P907, APPL ENVIRON MICROB
STAPLES RC, 1995, V134, P1, FEMS MICROBIOL LETT
SUAREZ T, 1996, V20, P529, MOL MICROBIOL
TENHAVE A, 2001, V33, P97, FUNGAL GENET BIOL
VERHOEFF K, 1988, V122, P327, J PHYTOPATHOL
WATSON N, 1992, V174, P530, J BACTERIOL
WUBBEN JP, 2000, V37, P152, CURR GENET
YAKOBY N, 2000, V66, P1026, APPL ENVIRON MICROB

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07557483 Genuine Article#: 180UM Number of References: 16
Title: Solid-phase synthesis of potential aspartic acid protease inhibitors containing a hydroxyethylamine isostere
Author(s): Zhou JL (REPRINT) ; Termin A; Wayland M; Tarby CM
Corporate Source: COMBICHEM INC,DEPT MED CHEM, 9050 CAMINO SANTA FE/SAN DIEGO//CA/92121 (REPRINT)
Journal: TETRAHEDRON LETTERS, 1999, V40, N14 (APR 2), P2729-2732
ISSN: 0040-4039 Publication date: 19990402
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND
Language: English Document Type: ARTICLE
Geographic Location: USA
Subfile: CC PHYS--Current Contents, Physical, Chemical & Earth Sciences; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: CHEMISTRY, ORGANIC
Abstract: A series of 1,3-diamino-2-propanol derivatives have been synthesized on solid phase as potential aspartic acid protease inhibitors. The developed methodology allows the incorporation of either an alkyl group or H at the R-2 site of hydroxyethylamine isostere. (C) 1999 Elsevier Science Ltd. All rights reserved.
Descriptors--Author Keywords: *aspartic acid protease ;* inhibitors ; hydroxyethylamine isostere ; solid-phase synthesis
Identifiers--KeyWord Plus(R): HIV PROTEASE
Cited References:
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2/9/14 (Item 3 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
(c) 2005 Inst for Sci Info. All rts. reserv.

04901284 Genuine Article#: UQ420 Number of References: 31
Title: THE PRIMARY STRUCTURE AND ENZYMATIC-PROPERTIES OF PORCINE PROCHYMOSIN AND CHYMOSENIN
Author(s): HOUEN G; MADSEN MT; HARLOW KW; LONBLAD P; FOLTMANN B
Corporate Source: STATENS SERUM INST,DEPT AUTOIMMUNOL,ARTILLERIVEJ 5/DK-2300 COPENHAGEN S//DENMARK//; UNIV COPENHAGEN,DEPT PROT CHEM/DK-1353 COPENHAGEN K//DENMARK//
Journal: INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY, 1996, V28, N6 (JUN), P667-675
ISSN: 1357-2725
Language: ENGLISH Document Type: ARTICLE

Geographic Location: DENMARK

Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences

Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY; CELL BIOLOGY

Abstract: Preliminary investigations by N-terminal sequence analysis showed that pig and calf chymosin possessed 80% amino acid sequence identity but showed considerable differences in their enzymatic properties. A comparison of their structures may therefore contribute to an understanding of the significance of the amino acid residues responsible for the differences in these properties. Pig chymosin was extracted from the stomachs of pigs of less than 3 weeks of age, and was purified by ion exchange chromatography. Half of the primary structure was determined by amino acid sequencing and the complete structure was deduced from a cloned chymosin cDNA. Results showed that the zymogen showed 81% sequence identity with calf prochymosin and 57% identity with pig pepsinogen A. The size of the propart and location of the residue which becomes the N-terminus in the active molecule were the same in the prochymosins. The maximum general proteolytic activity at pH 3.5 of pig chymosin was 2-3% of that of the activity of pig pepsin A at pH 2, whereas the milk clotting activity relative to the general proteolytic activity of pig chymosin was much higher than that of calf chymosin. Agar gel electrophoresis at pH 5.3 of stomach extracts of individual pigs showed the existence of two predominant genetic variants of zymogen and enzyme. The two variants could not be distinguished by amino acid composition or N-terminal sequencing, and no differences in the enzymatic properties of the genetic variants were observed. It was concluded that of the residues that participate in the substrate binding, calf and pig chymosin differ in the following positions (pig pepsin numbering, subsites in parentheses): Ser 12 Thr (S-4), Leu 30 Val (S-1/S-3), His 74 Gln (S'(2)), Val 111 Ile (S-1/S-3), Lys 220 Met (S-4). With regard to the low general proteolytic activity of pig chymosin, the substitution Asp 303 Val relative to calf chymosin may contribute to an explanation of this. (C) 1996 Elsevier Science Ltd

Descriptors--Author Keywords: PROCHYMOSIN ; *ASPARTIC ACID PROTEASE ; *PIG ; CDNA ; PRIMARY STRUCTURE

Identifiers--KeyWords Plus: POLYACRYLAMIDE-GEL ELECTROPHORESIS; MOLECULAR-CLONING; PROTEINS; PEPSIN; MUTAGENESIS; RESOLUTION; PROTEASES; MEMBRANES; SEQUENCE; PIGS

Research Fronts: 94-3070 001 (RAT SKELETAL-MUSCLE; DEVELOPMENTAL REGULATION; YEAST SACCHAROMYCES-CEREVISIAE)

94-4806 001 (GENE ORGANIZATION; LONG-CHAIN FATTY-ACID TRANSPORT; TRANSCRIPTION FACTOR)

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2/9/15 (Item 1 from file: 71)
DIALOG(R) File 71:ELSEVIER BIOBASE
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00487022 96180987

HIV protease and the pathogenesis of AIDS

Goldberg B.; Stricker R.B.

ADDRESS: Dr. R.B. Stricker, 450 Sutter Street, San Francisco, CA 94108,
United States

Journal: Research in Virology, 147/6 (375-379), 1996, France

PUBLICATION DATE: 19960000

CODEN: RESVE

ISSN: 0923-2516

DOCUMENT TYPE: Short Survey

LANGUAGES: English SUMMARY LANGUAGES: French

DESCRIPTORS:

AIDS; HIV; Protease; *Aspartic acid protease*; Protease inhibitors;
Pathogenesis; Hypothesis

CLASSIFICATION CODE AND DESCRIPTION:

86.7.7.4 - IMMUNOLOGY AND INFECTIOUS DISEASES / IMMUNITY TO INFECTION /
AIDS and HIV / Pathogenesis and syndrome manifestations

82.8.3 - PROTEIN BIOCHEMISTRY / HYDROLYTIC ENZYMES (EC 3.) / Proteases,
Peptidases and Proteinases

82.12.7.4 - PROTEIN BIOCHEMISTRY / OTHER PROTEINS / Microbial Proteins /
Viral

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Logon file405 09may05 14:44:00

*** ANNOUNCEMENT ***

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***German Patents Fulltext (File 324)

***Beilstein Abstracts (File 393)

***Beilstein Facts (File 390)

***Beilstein Reactions (File 391)

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***Medline (Files 154 & 155)

***ToxFile (File 156)

RESUMED UPDATING

***Canadian Business and Current Affairs (262)

***CorpTech (559)

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***Health News Daily (43)

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***FDC Reports (186/187)

***NDA Pipeline: New Drugs (189)

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KWIC is set to 50.

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5,159,143,358,340,344,348,447,73,155,349,266,10,34,434,42,43,50,65,71,91,94,14
4,198,304,370,467,444,357,156,157.

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      $0.00    0.213 DialUnits FileHomeBase
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$0.06  Estimated cost this search
$0.06  Estimated total session cost   0.213 DialUnits
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File 5:Biosis Previews(R) 1969-2005/May W1
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File 358:Current BioTech Abs 1983-2005/Apr
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File 94:JICST-EPlus 1985-2005/Mar W3
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File 304:The Merck Index Online(SM) 2004/S2
(c) 2004 MERCK & CO. INC.

***File 304: File is now current to the 13th edition of The Merck Index**

File 370:Science 1996-1999/Jul W3
(c) 1999 AAAS

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File 467:ExtraMED(tm) 2000/Dec
(c) 2001 Informania Ltd.

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? s	aspartic enzyme	
	S1	1 ASPARTIC ENZYME
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1/9/1 (Item 1 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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0013972220 BIOSIS NO.: 200200565731

Comparative digestive enzyme ontogeny in two marine larval fishes: Pacific threadfin (*Polydactylus sexfilis*) and bluefin trevally (*Caranx melampygus*)

AUTHOR: Kim Bong G; Divakaran S; Brown Christopher L (Reprint); Ostrowski Anthony C

AUTHOR ADDRESS: Marine Biology Program, Florida International University,
3000 NE 151st St., North Miami Beach, FL, 33181, USA**USA

JOURNAL: Fish Physiology and Biochemistry 24 (3): p225-241 April, 2001
2001

MEDIUM: print

ISSN: 0920-1742

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The specific activity of digestive enzymes; aspartic and serine protease, collagenase, lipase, acid and alkaline amylase, acid and alkaline phosphatase, and chitinase was assayed throughout early development in two species of marine fishes: the Pacific threadfin (*Polydactylus sexfilis*) and bluefin trevally (*Caranx melampygus*). Specific enzyme activities were determined on whole larval extracts sampled at selected stages of development, from day 0 to day 30 post-hatching. Similar developmental patterns of enzyme specific activity were observed in the two species, although differences in timing, amplitude and effects of first feeding were noted. Amylase activity increased prior to first feeding, peaking at the middle of the larval period, and becoming nearly undetectable by the time of larval-to-juvenile metamorphosis. Serine protease, collagenase, lipase and alkaline (and acid for threadfin) phosphatase activities increased gradually, followed by sharp increases to a plateau during the second half of larval development. Aspartic protease and chitinase activities, in addition to acid phosphatase (for trevally), were low to undetectable in the first half of development, increasing through metamorphosis. In the trevally only, this group of enzymes exhibited high activity levels at the time of hatching, followed by a precipitous drop. Species-dependent differences in enzyme specific activity at first feeding may have been a result of differences in yolk utilization. These results, taken in the context of earlier reports, lead us to conclude that carbohydrate utilization may play a significant role in the earlier phases of development among some marine larvae, followed by a shift to protein and lipid utilization.

REGISTRY NUMBERS: 9001-77-8: acid phosphatase; 9001-78-9: alkaline phosphatase; 9001-06-3: chitinase; 9001-12-1: collagenase; 9001-62-1: lipase; 37259-58-8: serine protease

DESCRIPTORS:

MAJOR CONCEPTS: Digestive System--Ingestion and Assimilation; Enzymology
--Biochemistry and Molecular Biophysics

BIOSYSTEMATIC NAMES: Osteichthyes--Pisces, Vertebrata, Chordata, Animalia

ORGANISMS: Caranx melampygus {bluefin trevally} (Osteichthyes);
Polydactylus sexfilis {Pacific threadfin} (Osteichthyes)

COMMON TAXONOMIC TERMS: Animals; Chordates; Fish; Nonhuman Vertebrates;
Vertebrates

CHEMICALS & BIOCHEMICALS: acid phosphatase; alkaline amylase; alkaline
phosphatase; *aspartic enzyme*--digestive enzyme; chitinase;
collagenase; lipase; serine protease--digestive enzyme

METHODS & EQUIPMENT: carbohydrate utilization assay--analytical method

MISCELLANEOUS TERMS: digestive enzyme ontogeny; larval-to-juvenile
metamorphosis

CONCEPT CODES:

10802 Enzymes - General and comparative studies: coenzymes
14004 Digestive system - Physiology and biochemistry

BIOSYSTEMATIC CODES:

85206 Osteichthyes
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S1	1	ASPARTIC ENZYME
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